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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,456	ZAUDERER ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-122 and 127-131* is/are pending in the application.

4a) Of the above claim(s) *85-87,98,100-102 and 104-106* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84,88-97,99,103,107-122 and 127-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed July 25, 2006 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 84-122 and 127-131 were pending. Applicants amended claim 90. No claims were added or canceled. Claims 85-87, 98, 100-102 and 104-106 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 84, 88-97, 99, 103, 107-122 and 127-131 are examined on the merits in this action.

Withdrawn Objections/Rejections

4. The objection to claim 90 is withdrawn in view of Applicants' amendments thereto. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 103

5. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**)

and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**) and Waterhouse et al. (Waterhouse, P.; Griffiths, A.D.; Johnson, K.S.; Winger, G. "Combinatorial infection and in vivo recombination: a strategy for making large phage antibody repertoires" *Nucleic Acids Research*, **1993**, 21, 9, 2265-2266).

For ***claims 84, 88, 96-97, 113, 117***, Rowlands et al. (see entire document) teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). For example, Rowlands et al. teach **[a-c]** the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the

medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Alternatively, the Examiner contends that the phrase "wherein said second immunoglobulin subunit polypeptide is "capable of" combining with said first immunoglobulin subunit polypeptide to from an immunoglobulin molecule (e.g., see claim 84, step (b)(iii)) has not been afforded any patentable weight. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138, 141.

In addition, Rowlands et al. disclose **[d]** contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose **[e]** recovering the vaccinia virus

vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

For ***claim 103***, Rowlands et al. disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

The prior art teachings of Rowlands et al. differ from the claimed invention as follows:

For ***claim 84***, Rowlands et al. are deficient in that they do not specifically teach the use of a "library" of first/second polynucleotides.

For ***claims 89-91***, Rowlands et al. do not disclose repetitive steps for "biopanning" a library.

For ***claims 92-95***, Rowlands et al. do not provide "isolating" steps.

For ***claim 99***, Rowlands et al. do not disclose an MOI of 1.

For ***claim 107, 110, 127-131***, Rowlands et al. do not disclose method steps for "tri-molecular" recombination.

For ***claims 108-109, 111-112***, Rowlands et al. do not disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 114-116, 118-120***, Rowlands et al. do not disclose the use of virus

"pools."

However, Zauderer et al. and Waterhouse et al. teach the following limitations that are deficient in Rowlands et al.:

For ***claim 84***, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52; see also Zauderer et al., pages 49 and 50 wherein "multiple" libraries are produced; see also constructs in figure 2). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98,

"Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors, contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claims 107, 110, 127-131***, Zauderer et al. disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through

page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

It would have been *prima facie* obvious to of ordinary skill in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors

disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"; see also page 52 of Zauderer, middle paragraph, "The above-described tri-molecular recombination strategy yields close to 100% viral recombinants. This is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells. This latter procedure yields viral recombinants at a frequency of the order of only 0.1%."). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the

"associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al. In addition, Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody").

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered including all exhibits and/or declarations (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the

above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Applicants respectfully submit that, for the reasons discussed in the previously filed replies ... the present invention is not obvious over Rowlands in view of Zauderer and Waterhouse" (e.g., see 7/25/06 Response, page 18-21, especially page 21, first full paragraph).

[2] Applicants argue, "Applicants respectfully maintain that one of ordinary skill in the art would not have had a reasonable expectation of success ... Even if it is reasonable to conclude that one of ordinary skill in the art would know in view of Rowlands how to express an antibody, and would know in view of Zauderer how to make and use a vaccinia virus expression library, it does not follow that the artisan could, with a reasonable expectation of success, arrive at a method of selecting polynucleotides encoding antigen-specific immunoglobulins by introducing two libraries of vaccinia virus vectors into mammalian host cells. This gap in logic is highlighted by the Storkus Declaration, filed on July 21, 2005, wherein Dr. Storkus indicated that the expression of a single antibody as in Rowlands is far simpler than expression of pairs of immunoglobulin chains from two separate libraries, and that assembling separate chains from two libraries is a different concern than expressing one library as in Zauderer. Storkus Declaration at page 5 ... Applicants agree that Zauderer does not state that tri-molecular recombination should be limited to expressing "everything but antibodies." See Office Action at page 27. But the fact that Zauderer does not say that the disclosed libraries cannot be used for expressing immunoglobulins is not the same as the reference affirmatively saying that such libraries can be used for expressing immunoglobulins. By the Examiner's reasoning, any

reference that does not explicitly exclude or disclaim a particular feature could be said to teach that feature (i.e., if "X" is not explicitly disclaimed in the reference, then the reference teaches "X"). This logic is not correct. A *prima facie* showing of obviousness requires that the cited references teach every element of the claimed invention; it is not sufficient to merely show that the references do not expressly exclude a particular element. Thus, not only was there no reasonable expectation of success in combining Rowlands and Zauderer, as discussed in greater detail, infra, the cited references do not even teach every element of the claimed invention" (e.g., see 7/25/06 Response, pages 21-24).

[3] Applicants continue with the Storkus Declaration stating, "Dr. Storkus indicated that a eukaryotic cell was thought to be impractical for screening a sufficient number of eukaryotic cell to find an antibody that had specificity for a specific antigen of interest ... Hence, the limits on the ability to screen eukaryotic host cells as opposed to phage particles would have been considered an obstacle to the reasonable expectation of success in arriving at the claimed methods" (e.g., see 7/25/06 Response, paragraph bridging pages 24 and 25).

[4] Applicants continue to argue that *In re Vaeck* supports their position because the Examiner has "disregard[ed] the key fact that Rowlands describes only the expression of a single heavy chain and a single light chain from vaccinia virus vectors. This does not show that one of ordinary skill in the art could predict how infecting a library of heavy and a library of light chains in a mammalian host cells would work" (e.g., see 7/25/06 Response, pages 26 and 27, especially page 27, paragraph).

[5] Applicants reiterate there previous arguments that "one of ordinary skill in the art would not have even been motivated to combine these references" (e.g., see 7/25/06 Response,

pages 28 and 29).

[6] Applicants again argue that the Office has again failed to appreciate the cited references as a whole stating, for example, "features of the claimed invention have been selectively plucked from the cited references and pieced together by the Examiner to assert that the claimed invention is obvious" (e.g., see 7/25/06 Response, page 29 and 30, especially paragraph bridging pages 29 and 30; see also page 36, last full paragraph wherein this "gist" argument has been repeated).

[7] Applicants argue that the Office is not properly considering the Waterhouse reference as a whole citing *In re Hedges* and further state, "One of ordinary skill in the art would look to all of these aspects of Waterhouse in determining whether the method of selecting a polynucleotide encoding an immunoglobulin fragment from the phage display libraries described therein could be performed in a vaccinia virus system" (e.g., see 7/25/06 Response, page 30).

[8] Applicants argue, "To the contrary, the benefits that the Examiner indicates are implied [e.g., larger libraries → stronger antibodies] by Waterhouse were thought to be dependent on the type of expression system" and cite the Storkus Declaration in support of this contention, "the throughput for screening phage exceeded the expected throughput for screening libraries expressed in eukaryotic cells by as much as four orders of magnitude ... antibody fragments expressed in phage . . . are assembled in the periplasmic space [of the prokaryotic host cell]. The conditions of assembly in the eukaryotic cytoplasm are far different from those that apply in the periplasmic space and it could not be known what effect this would have on antibody assembly." Applicants conclude, "Thus, the size of the library that could be screened and the characteristics of heavy and light chain assembly were thought to be dependent on

whether the expression system was prokaryotic (e.g., bacterial) or eukaryotic (e.g., mammalian)" (e.g., see 7/25/06 Response, page 31).

[9] Applicants argue, "Waterhouse would be viewed by one of ordinary skill in the art, the reference actually teaches away from the claimed invention because it emphasizes features that one of ordinary skill in the art would not have associated with eukaryotic expression systems ... [an] ability to generate and screen large libraries" (e.g., see 7/25/06 Response, page 32, paragraph 1).

[10] Applicants argue, "the Examiner is [impermissibly] focusing on the notion that features of the method for selecting antibody fragments from a prokaryotic phage library expression system, as disclosed in Waterhouse, can merely be substituted into the method of expressing a single antibody heavy and light from vaccinia virus vectors as in Rowlands and/or the expression of one vaccinia virus library as in Zauderer to arrive at the present claimed methods" and cites *Hybritech* in support of this position (e.g., see 7/25/06 Response, pages 32 and 33, especially page 33, paragraph 2).

[11] Applicants argue that "obviousness to try" is not the standard and further stating, "[a]t the very most, the combination of Rowlands, Zauderer and Waterhouse might be an invitation to try selecting polynucleotides encoding an antigen-specific immunoglobulin molecule or fragment thereof in eukaryotic cells as in the present invention ... Even if, as the Office asserts, one of ordinary skill in the art would know which parameters are critical to express an antibody in a eukaryotic cell based on Rowlands, and which parameters are critical to form a library in eukaryotic cells based on Zauderer, one of ordinary skill of art would not know what parameters are critical to express two libraries in eukaryotic cells and select from them

polynucleotides encoding antigen specific immunoglobulin molecules" (e.g., see 7/25/06 Response, pages 33-35).

[12] Applicants argue, that the cited references do not teach every limitation of the claimed invention stating, "that this combination of references does not teach or suggest all of the elements of the claimed invention because they do not teach or suggest the introduction of two libraries of polynucleotides constructed in vaccinia virus vectors into eukaryotic cells ... contrary to the Examiner's assertions, the antibodies and antibody libraries produced by phage display would not necessarily be the same as those produced by the claimed invention ... As noted by the present specification, the phage display strategy "requires that complementarity determining regions (CDRs) of the expressed immunoglobulin fragment be synthesized and fold properly in bacterial cells. Many antigen binding regions, however, are difficult to assemble correctly as a fusion protein in bacterial cells. In addition, the protein will not undergo normal eukaryotic post-translational modifications. As a result, [the phage display] method imposes a different selective filter on the antibody specificities that can be obtained." Specification at page 4" (e.g., see 7/25/06 response, pages 35-37, especially paragraph bridging pages 36 and 37).

[13] Applicants argue that the office is using impermissible hindsight stating, "It is not sufficient to show that both Zauderer and Rowlands disclose uses of vaccinia virus vectors, especially since the vectors are used for different purposes in each reference and Zauderer does not teach or suggest screening a library of immunoglobulins or, indeed, using two such libraries. Likewise, it is not sufficient to show that Rowlands and Waterhouse both deal with antibodies, especially considering that Rowlands describes a method of expressing a single antibody in a mammalian cell and Waterhouse describes screening a phage library of antibody fragments

expressed in prokaryotic cells (e.g., see 7/25/06 Response, pages 37 and 38, especially page 38, first full paragraph).

[14] Applicants argue that *In re Fine* is still "relevant" to the present case stating, "Analogous to *Fine*, the present invention diverges from Waterhouse and teaches advantages not appreciated or contemplated by it. Namely, the present invention allows direct expression and selection of polynucleotides encoding antigen-specific immunoglobulins by introducing two separate vaccinia virus expression libraries of heavy and light chains into mammalian host cells ... ." (e.g., see pages 7/25/06 Response, 38-41, especially last paragraph on page 40).

[15] Applicants argue that their arguments and evidence are commensurate in scope with the claims stating, "Dr. Storkus stated that he 'thought specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a specific antigen of interest.' ... Furthermore, the fact that selection of antibody fragments had been performed in phage did not convince Dr. Storkus that eukaryotic cells could be used to screen for antigen-specific antibodies because of the limitations on screening throughput for eukaryotic cells compared to phage particles. Also, Dr. Storkus indicates that it was not clear, just because assembly of two separate immunoglobulin chain fragments in the periplasmic space of a prokaryotic cell could be achieved, that assembly in the cytoplasm of a eukaryotic cell would also occur to allow selection of polynucleotides encoding an antigen-specific immunoglobulin" (e.g., see 7/25/06 Response, pages 41 and 42, especially page 42, paragraph 1).

[16] Applicants further submit, "that the claims are directed to a method of selecting polynucleotides encoding an immunoglobulin heavy or light chain, which, as part of an

immunoglobulin molecule, is specific for an antigen. If the immunoglobulin heavy and light chains are not capable of pairing together in the mammalian host cell ... then no antigen-specific immunoglobulin molecules could bind the antigen of interest or be detected as part of a specific antigen-antibody complex, and vaccinia virus vectors containing polynucleotides encoding the immunoglobulin subunit polypeptides could not be recovered according to the claimed method" (e.g., see 7/25/06 Response, page 42, paragraph 2).

[17] Applicants argue, "The expectation of success is not shown to be reasonable by the disclosure of Rowlands because the Campath-1H heavy and light chains described in Rowlands were already known to recognize antigen when paired together. This is qualitatively different than introducing multiple immunoglobulin heavy and light chains that must be capable of pairing to form immunoglobulin molecules and selecting polynucleotides encoding an antigen-specific immunoglobulin" (e.g., see 7/25/06 Response, paragraph bridging pages 42 and 43).

[18] Applicants argue, "Applicants respectfully submit that the Office is basing its assessment of long-felt need on its improper distillation of the "gist" of the invention (i.e., a method of producing an antibody), rather than considering the evidence of the Zauderer Declaration in assessing a long-felt need with respect to the claimed invention. The claims are directed to a method of selecting polynucleotides encoding an antigen-specific human immunoglobulin molecule. Full immunoglobulins produced, for example, from fragments selected by phage display that no longer recognize target antigen once they are removed from the phage context are not antigen-specific. See Zauderer Declaration at page 7. Furthermore, antibodies produced in prokaryotic cells are not processed or assembled in the same manner as antibodies expressed in eukaryotic (e.g., mammalian) cells, and therefore may lose antigen

specificity due to improper folding. Id. at pages 4- 5. As evidenced by Exhibits A2 and B2-B4 and as discussed in greater detail, below, the advantages offered by the present invention were desired by those in the art. Thus, Applicants respectfully submit that the Zauderer Declaration and the Exhibits of record are commensurate in scope with the claimed invention in showing a long-felt need" (e.g., 7/25/06 Response, pages 43 and 44, especially bridging paragraph).

[19] Applicants argue that the objective evidence of non-obviousness has not been properly considered stating, "Applicants respectfully submit that the quotation from Exhibit A2, as well as the rest of the document, represents a survey indicating that, as of 2001, the existing antibody selection technologies (e.g., phage display and transgenic mice) were not satisfactory to those of skill in the art who were looking for antibody selection platforms that could be used to identify antigen specific antibodies, including antibodies to targets that would not elicit an immune response in a transgenic mouse and antibodies that could also be used in functional assays without having to reclone fragments isolated, e.g., by phage display, into a full antibody structure. See Exhibit A2 at page 34." (e.g., see 7/25/06 Response, pages 44 and 45, especially page 45, first full paragraph).

[20] Applicants argue, "Exhibits B2-B4 provide evidence that the claimed methods are recognized in the art as meeting the needs of these representative companies in the area of antibody discovery. The Examiner asserts that OPi's statements in Exhibit B2 are deficient because "OPi's statement doesn't even refer to any of the claimed features such as the use of a vaccinia virus eukaryotic expression system." However, Exhibit B4 does specifically indicate that the library-based technology is in vaccina vectors. See Exhibit B4, last paragraph. The Examiner also asserts that the Exhibits are deficient because "the failure to solve a long-felt need

may be due to factors such as a lack of interest or lack of appreciation of an invention's potential or marketability rather than want of technical know-how." Office Action at page 34 (citations omitted). Applicants point to Exhibit A2, which shows that those of ordinary skill in the art were interested in a technology with the features of the claimed invention." (e.g., see 7/25/06 Response, page 46, paragraph 1).

[21] Applicants argue, "At pages 40-41 of the Office Action, the Examiner asserts that Exhibits B2-B4 are insufficient rebuttal evidence because they do not show a nexus between the claimed invention and the strategic alliances based on use of the technology. In particular, the points to the specific language of Exhibit B4 and asserts that Applicants' claims are not limited to "bivalent, monoclonal fully human antibodies." Applicants' claims are directed to a method of selecting polynucleotides that encode an antigen-specific human immunoglobulin molecule. The specification as filed defines "immunoglobulin molecule" as "a complete, bi-molecular immunoglobulin, i. e., generally comprising four 'subunit polypeptides, 'i.e., two identical heavy chains and two identical light chains." Specification at Paragraph 0057." (e.g., see 7/25/06 Response, page 46, middle paragraph).

[22] Applicants argue, "The Examiner asserts that "while no details of the strategic alliances are given, it may very well be, for example, that the competitors decided, for business and/or financial reasons, not to pursue other opportunities. The decision not to pursue one opportunity as opposed to another may be dictated by many factors other than a need for the claimed features of Applicants' invention." Office Action at page 42. In response, Applicants point to Exhibit B2, in which OPi's CEO states that "Vaccinex's innovative antibody discovery technology will enable us to make a technological leap to develop new fully human antibodies

aiming at treating haematological diseases." Exhibit B2, 3rd Paragraph (emphasis added)" (e.g., see 7/25/06 Response, bottom page 45).

[23] Applicants argue, "To the extent that the Examiner asserts that the claims are not limited to haematological diseases, see Office Action at page 40, Applicants respectfully reiterate that, while each of the representative business organizations in Exhibits B2-B4 has, at a certain level of specificity, its own uses for the claimed invention (e.g., developing antibodies to its own antigenic targets of interest), the diversity of uses for the claimed invention among various companies is evidence that the claimed invention has broader applicability than any of the single uses of any one company. Therefore, Applicants respectfully submit that the Exhibits of record provide evidence of a long-felt need for the methods of the present invention." (e.g., see paragraph bridging pages 46 and 47)" (e.g., see page 47, paragraph 1).

[24] Applicants "summarize" previous arguments (e.g., see page 47 and 48).

These arguments are not found persuasive fore the following reasons:

[1 and 24] To the extent that Applicants are simply repeating their previous arguments, those arguments were adequately addressed in one of the previous office actions or one of the cited sections cited by Applicants, which are incorporated in their entirety herein by reference.

[2] The Examiner has never asserted that if "X" is not explicitly disclaimed in the reference, then the reference necessarily teaches "X" as purported (see above). To the contrary, the previous office action merely reads, "in considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom." *In re Preda*, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968) (A process for catalytically producing carbon disulfide

by reacting sulfur vapor and methane in the presence of charcoal at a temperature of "about 750°-830°C" was found to be met by a reference which expressly taught the same process at 700°C because the reference recognized the possibility of using temperatures greater than 750°C. The reference disclosed that catalytic processes for converting methane with sulfur vapors into carbon disulfide at temperatures greater than 750°C (albeit without charcoal) was known, and that 700°C was "much lower than had previously proved feasible."); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976) (Reference disclosure of a compound where the R-S-R'; portion has "at least one methylene group attached to the sulfur atom" implies that the other R group attached to the sulfur atom can be other than methylene and therefore suggests asymmetric dialkyl moieties.")" (i.e., see 4/21/06 Office action, page 17, section [2]). Thus, it is clear from the case law that if a reference does not explicitly teach "X", such a limitation may, nevertheless, be "inferred" from such a reference if one of skill in the art would reasonably expect this "X" limitation to flow from the reference and/or combination of references. Here, it can be "inferred" from Waterhouse et al. that in order to receive the benefit of simultaneous co-selection that two libraries are going to have to be introduced (i.e., heavy and light chains) into an expression system because co-selection would not occur without diversity in both the heavy (i.e., library 1) and light (i.e., library 2) chains. In addition, it can also be "inferred" that the advantages of co-selection would be just as applicable to mammalian systems as to prokaryotic systems because antibody selection depends on the structure of the antibody, not the source from which it was obtained (i.e., an antibody produced in a eukaryotic host would have the exact same binding affinity as an identical antibody produced in a prokaryotic host for a given antigen). This teaching is further "augmented" by Rowlands et al. who present an facile method for

expressing antibodies (both heavy and light chains) in eukaryotic systems and Zauderer et al. who present a facile method for producing "libraries of proteins" in these same hosts. Therefore, the combination of references, clearly teaches every element of the claimed invention.

With respect to Applicants' "reasonable expectation of success" argument, the Examiner again notes that obviousness does not require absolute predictability of success; rather, all that is required for obviousness under § 103 is a "reasonable expectation of success." *In re O'Farrell*, 853 F.2d at 903-904 [7 USPQ2d at 1681]. Here, Rowlands et al. teach a method for producing antibodies in vaccinia infected "mammalian" cells (e.g., see Rowlands et al. page 4, paragraph 2; see also paragraph bridging pages 7-8). Thus, the conclusion that a person of skill in the art would know how to express an antibody in a "mammalian" cell is reasonable. Zauderer et al. teach how to make and/or use a library of proteins using a vaccinia virus vector like the vaccinia virus vector disclosed by Rowlands (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). Thus, the conclusion that a person of skill in the art would know how to make and/or use a library of proteins, including antibodies, with a vaccinia virus is reasonable. That is, the Zauderer et al. reference never states or indicates in any way that the use of tri-molecular recombination should somehow limited to expressing only one particular class of proteins (i.e., everything but Applicants' claimed antibodies). Finally, Waterhouse et al. teach the co-selection of a library of heavy and light chains (i.e., the use of two libraries) and thus a conclusion that these two libraries would be "capable" of combining together is reasonable since co-selection

could not be performed without it. Alternatively, the Examiner contends that the phrase "wherein said second immunoglobulin subunit polypeptide is capable of combining with said first immunoglobulin subunit polypeptide to from an immunoglobulin molecule (e.g., see claim 84, step (b)(iii)) should not be afforded any patentable weight. It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138, 141. Therefore, Applicants' arguments are moot.

Finally, the Examiner note that all of Applicants' arguments are simply not commensurate in scope with the claims. For example, the Storkus Declaration to which Applicants' allude merely refers to "efficient" selection, which is not at issue in this case. That is, the features upon which applicants relied in the Storkus declaration (i.e., "efficient" selection, libraries that are not "poorly matched", the use of "random" pairs of immunoglobulins) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, the declaration is not commensurate in scope with the claims (e.g., see In re Grasselli, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983) (Claims were directed to certain catalysts containing an alkali metal. Evidence presented to rebut an obviousness rejection compared catalysts containing sodium with the prior art. The court held this evidence insufficient to rebut the prima facie case because experiments limited to sodium were not commensurate in scope with the claims); see also *In re Tiffin and Erdman*, 171 USPQ 294 (CCPA 1971) and cases cited therein; see also MPEP § 716.02(d). That is, the claims do not require "efficient" introduction of libraries into hosts cells, "efficient" selection, libraries that are

not "poorly matched", the use of "random" pairs of immunoglobulins or the production of "good" antibodies as Dr. Storkus contends. Independent claim 84, for example, does not set any requirements on the "efficiency" of selection or the resultant quality of the antibody libraries produced. That is, the Storkus Declaration never states we wouldn't expect "any" matching to occur whatsoever but, rather, only "efficient" matching that will lead to "good" antibodies. In addition, the Examiner again notes that Applicants' claimed scope encompasses "low efficiency" methods that generate "poor" antibodies (e.g., see 12/7/04 Response, page 22, "While the specification does indicate that direct ligation results in a relatively low recombination efficiency and titer ... it does not say that methods such as direct ligation or modified homologous recombination [which are included within the scope of Applicants' invention] cannot be used to generate vaccinia virus expression libraries"; see also page 25, first full paragraph, "... direct ligation and modified homologous recombination may be less efficient than tri-molecular recombination ... [however] the specification does not say that they cannot be used") (emphasis added). Therefore, the Storkus declaration is simply not on point.

[3] Again, Applicants' arguments (and the Storkus Declaration to which Applicants refer) are not commensurate in scope with the claims (see **[2]** above). The claims only require that the second immunoglobulin subunit polypeptide is "capable" of combining with said first immunoglobulin (e.g., see claim 84, step (b)(iii)). Therefore, Applicants' arguments are moot.

[4] The Examiner respectfully disagrees. It is not the Examiner who is "disregarding" key facts but, rather, Applicants. For example, Applicants only claim that the two libraries are "capable" of combining (e.g., see claim 84, step (b)(iii)), which is not a patentable limitation and thus cannot be relied upon to distinguish the prior art (e.g., see *In re Hutchison* analysis above).

Therefore, Applicants arguments are moot. In addition, even if, assuming arguendo, the "capable of" language could be interpreted as a patentable limitation (which is not the case), Waterhouse et al. proves that the antibodies are "capable of" combining (e.g., see paragraph bridging pages 2265 and 2266 wherein the libraries were actually combined).

In addition, as previously noted, Judge Rich stated in *Vaeck*, "it is only in recent years that the biology of cyanobacteria has been clarified ... Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene." See Id. at 1443. That is, when the CAFC assessed the prior art they took into account the high degree of unpredictability surrounding the poorly characterized cyanobacteria to make their obviousness determination. Judge Rich noted that the cyanobacteria had only recently been reclassified as a unique type of bacteria rather than blue-green algae. See Id. Thus, it was under these circumstances that the insertion of a Bacillus gene into cyanobacteria was held to be non-obvious. A person of ordinary skill in the art simply wouldn't be able to predict how the cyanobacteria would respond to the introduction of a Bacillus gene given how little was known about these newly classified prokaryotic hosts. That is definitely not the case here. Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully

functional antibody") (emphasis added). Zauderer et al. present a facile method for producing libraries in the same host. Thus, *In re Vaeck* simply isn't on point because we're not dealing with systems that are poorly understood.

[5] In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies

"should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B" (i.e., producing two libraries simultaneously).

Furthermore, in response to applicant's arguments against the Rowlands reference individually (or in combination with Zauderer), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, two separate expression libraries of both immunoglobulin light and heavy chains is clearly suggested by Waterhouse (e.g., see section [2] above).

[6] The Examiner agrees that the claimed invention must be considered as a whole in accordance with MPEP § 2141.02. However, the Examiner contends that this requirement has been adequately met. For example, the Examiner has not boiled the claimed invention down to a "gist" or a "thrust" of the invention as was shown to be improper in cases like Bausch & Lomb v. Barnes-*Hind/Hydrocurve, Inc.*, 796 F.2d 443, 447-49, 230 USPQ 416, 419-20 (Fed. Cir. 1986), cert. denied, 484 U.S. 823 (1987); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984); and *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593 (Fed. Cir.), cert. denied, 481 U.S. 1052 (1987). See, for example, MPEP § 2141.02, section II. For example, the "two" libraries are taught by the "combined" references as outlined in the rejection above. That is, it would be obvious to express "two" libraries of antibodies (heavy in light chains) in the mammalian expression system disclosed by Rowlands et al. for the purposes of screening for higher affinity antibodies as taught by the combined teachings of Zauderer et al.

and Waterhouse et al. Thus, the Examiner has not "disregarded the claimed features of introducing two vaccinia virus libraries encoding whole immunoglobulin heavy and light chains into mammalian host cells" (e.g., see 7/25/06 Response, paragraph bridging pages 29 and 30) but, to the contrary, it is Applicants who have failed to acknowledge this explicit recitation here and in the above rejection. In addition, the Examiner notes that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 425, 208 USPQ871, 881 (CCPA 1981). Here, as consistently noted in the above arguments and rejection, the three references clearly teach Applicants' claimed invention.

In addition, Applicants have not alleged or provided any evidence showing a failure to discover a source/cause problem (e.g., see MPEP § 2141.02, sections III and IV). Furthermore, the Examiner has taken into consideration all of the relevant "inherent" features as required, for example, by MPEP § 2141.02, section V (e.g., see above rejection, "Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence."). Finally, the Examiner notes that the previous office action also addressed all of Applicants' "teaching away" arguments as required by MPEP § 2141.02, section VI (e.g., see 4/21/06 Office action, page 25, paragraph 1, especially line 9, "No such "teaching away" exists here"). Therefore, Applicants' arguments are moot.

[7] This statement is not even consistent with Applicants' own specification, which clearly admits that a person of skill in the art would look, perhaps preferentially, to phage display. For example, Applicants state, "Previously, three general strategies have been employed to produce immunoglobulin molecules ... is to screen recombinant human antibody fragments displayed on bacteriophage [i.e., a person trying to make antibodies would have routinely looked to this discipline for guidance] ... Examples of phage display methods that can be used to make the antibodies include those disclosed in Brinkman ... Ames, R. S. ... Kettleborough, C. [etc.]" (e.g., see specification, paragraphs 9-11; see also paragraph 12 wherein Applicants' acknowledge that phage display can be used to produce human antibodies; see especially Example 3, paragraph 321 wherein Applicants expressly endorse the use of phage display as a teaching for vaccinia virus vectors i.e., they use the data provided by phage display (10^9 members will generate a strong binding affinity) to guide their vaccinia virus work). Therefore, Applicants' implicit argument that these two systems do not represent analogous art is without merit. Both papers deal with the production of antibodies and, as a result, represent analogous art (e.g., see In re Paulsen 31 USPQ2d 1671 (Fed. Cir. 1994) (A "clam style" fastening means is not "unique" to the computer industry and, as a result, a person of skill would consult other "mechanical" literature for a solution to this fastening problem).

Furthermore, to the extent Applicants are implicitly trying to argue again that, "using prokaryotic expression systems could not be extrapolated to eukaryotic cells because the conditions for assembly of immunoglobulins from light and heavy chains are different in the eukaryotic cytoplasm than in the periplasmic space of a bacterial host" (e.g., see 2/2/06 Response, page 27, paragraph 2 quoting Storkus Declaration, paragraph 4), the Examiner again

notes that that the Waterhouse et al. reference is not being relied upon for this purpose. The Examiner has never made such a contention and it is not at issue in this case. Waterhouse is being relied upon for the reasons set forth in the rejection, much the same way that Applicants' relied on "phage display" references in their specification (e.g., see Example 3). Again, the Examiner has never contended that the eukaryotic systems should somehow employ prokaryotic reaction conditions in some sort of hybrid expression system. The Waterhouse et al. reference, when take as a whole, impliedly shows that the production of two libraries (e.g., heavy and light chain) will lead to more favorable antibodies via a co-selection process regardless of how those antibodies are produced. Thus, Applicants' arguments are moot.

[8] Again, Applicants' arguments are not commensurate in scope with the claims. Applicants' are not claiming the use of only "large" libraries or "strong binding affinity" antibodies for "therapeutic" use.

In addition, the Storkus Declaration is ambiguous. For example, Dr. Storkus states, "At the time the idea for the present invention was presented to me, I did not think that antigen-specific antibodies could be efficiently selected from random libraries of immunoglobulin heavy and light chains expressed in eukaryotic cells in vitro because I thought specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a specific antigen of interest" (e.g., see Storkus Declaration, page 3, paragraph 7). However, Dr. Storkus never states at "what time" was the idea presented to him. Perhaps it was presented to him 20 years ago (i.e., phage display had been around since at least the mid 1980s as evidenced by the work of Smith) when tri-molecular recombination had not yet been invented (i.e., before

the Zauderer et al. reference). We don't know what Dr. Storkus would have stated at "the filing date of the application" as required. Thus, these statements provide no evidentiary support for Applicants.

In addition, this assertion of "relatively low frequency" in contradicted by the Zauderer et al., reference, the Waterhouse reference and Applicants' own specification. For example, Zauderer et al. state that they can "efficiently" produce libraries and even tout 100% conversion using the tri-molecular approach (e.g., see Zauderer et al., page Detailed Description of the Invention, especially paragraph bridging pages 14 and 15, "In one embodiment of the invention ... [i]mproved and modified vaccinia virus vectors for efficient construction of such DNA libraries using a "trimolecular recombination" approach are described to improve screening efficiency"; see also page 22, last full paragraph; see especially, page 52, middle paragraph, "The above-described tri-molecular recombination strategy yields close to 100% viral recombinants. This is a highly significant improvement over current methods for generating viral recombinants by transfection of a plasmid transfer vector into vaccinia virus infected cells. This latter procedure yields viral recombinants at a frequency of the order of only 0.1%."). Thus, Zauderer et al. explicitly state that they can "increase" their efficiency by exactly "four orders of magnitude" (i.e., 0.1% → 100%) as noted by Applicants above (emphasis added).

In addition, the Storkus declaration never states that adequate diversity could not be generated using "more than one" library. The declaration, instead, focuses on single chain Fv antibodies, which does not equate to the use of "two" libraries as set forth, for example, by Waterhouse et al. (e.g., see Waterhouse et al., paragraph bridging pages 2265 and 2266, "The process [i.e., the use of "two" libraries] appears to be highly efficient, and should allow the

creation of extremely large combinatorial repertoires, for example, by providing a light chain repertoire in A and a heavy chain repertoire in B. It should also facilitate the affinity maturation of antibodies selected from the large libraries by chain shuffling"; see also Applicants' admission in Example 3, "Previous work [i.e., the prior art] employing phage display methods has suggested that for many antigens a library that includes 10^9 immunoglobulin heavy and light chain combinations is of a sufficient size to select a relatively high affinity specific antibody. In principle, it is possible to construct a library with 10^9 recombinants each of which expresses a unique heavy chain and a unique light chain or a single chain construct with a combining site comprising variable regions of heavy and light chains. The most preferred method, however, is to generate this number of antibody combinations by constructing two libraries of 10^5 immunoglobulin heavy chains and 10^4 immunoglobulin light chains that can be co-expressed in all 10^9 possible combinations"). Thus, even Applicants admit that the prior art suggested the creation of larger libraries using "two" libraries of heavy (e.g., 10^5 members) and light (e.g., 10^4 members), which is position that is entirely consistent with the teachings of Waterhouse. Finally, the Examiner notes that although Dr. Storkus states that he thought "separate libraries would be poorly matched" in mammalian systems because, "[t]he conditions of assembly in the eukaryotic cytoplasm are far different from those that apply in the periplasmic space and it could not be known what effect this would have on antibody assembly" (e.g., see Storkus Declaration, pages 3 and 4, paragraph 7), Dr. Storkus never explains what the "far different" conditions are upon which the conclusion is based. Thus, there is no factual basis for this "poorly matched" assertion. Furthermore, Applicants are implicitly arguing against the 35 U.S.C. § 103 statute itself, which is impermissible. An obviousness rejection will, as practical mater, necessarily

assert the use of a secondary reference (or source) to teach the "new" conditions (i.e., limitations) that are deficient in the primary reference(s) (i.e., "two" libraries in a mammalian cell host in this case). Applicants cannot elevate the standard of non-obviousness under 35 U.S.C. § 103 to one of anticipation under 35 U.S.C. § 102. If "two" libraries in a mammalian host were found in one reference as suggested by Applicants that reference would "anticipate" the claimed invention. This was not the intention of Congress (e.g., see *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966)).

[9] It is not Waterhouse who "emphasizes" these features but, rather, Applicants. Furthermore, "a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend upon the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 478, 484 (1966)). Here, Waterhouse et al. teach that greater diversity can be generated using "two" libraries (i.e., heavy and light chain) as opposed to one. Furthermore, a person of skill in the art would understand that this is a "numerical" advantage (i.e., two is better than one) that would be independent of the system. Waterhouse, contrary to Applicants' assertions never states something like, "while the use of "two" libraries was found to be advantageous for phage display, it certainly wouldn't work for other systems like the vaccinia virus vectors disclosed in Zauderer or Rowlands." No such statements exist. This position is also support by In re Fine as

mentioned previously. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988), involved a system for measuring minute quantities of nitrogen presumably for the detection of drugs and explosives. The claims were rejected as being obvious over Eads in view Warnick. Eads disclosed a method for separating and identifying sulfur compounds. Warnick disclosed a process for detecting pollutants in the atmosphere by measuring the level of nitric oxide. The PTO held that it would have been prima facie obvious to substitute the nitric oxide detector of Warnick for the sulfur dioxide detector of Eads. On appeal, the Federal Circuit reversed noting that Eads deliberately sought to avoid the use of nitrogen because the sulfur detector was adversely affected by substantial quantities of nitrogen. Thus, according to the CAFC, "instead of suggesting that the system be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention." See Id. at 1599. Thus, In re Fine provides an example of a "teaching away" by disclosing that the presence of a claimed element, nitrogen, is undesirable. Thus, In re Fine is distinguishable from the present case. No such "teaching away" exists here. To the contrary, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as

glycosylation. This may be particularly important for genes of mammalian origin"). In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" (e.g., see Waterhouse et al., page 2265, paragraph 2; see also page 2265, column 1; see also paragraph bridging pages 2265-2266 wherein the usefulness of combinatorial antibody libraries is disclosed), which would encompass the "associated" heavy/light chains described by Rowlands et al. In addition, Waterhouse et al. also teach that larger "primary" repertoires of antibodies "should allow higher affinity fragments to be isolated" (e.g., see Waterhouse et al., page 2265, column 1, paragraph 1; see also page 2266, column 1, paragraph 1), which can be easily produced by varying providing "a light chain repertoire in A and a heavy chain repertoire in B."

[10] The Examiner maintains that Hybritech is not applicable here for the reasons of record (e.g., see pages 28 and 29 of the 4/21/06 office action, argument 11). Furthermore, the Examiner has never alleged the "mere" substitution as purported. Therefore, Applicants' arguments are moot.

[11] The Examiner respectfully disagrees. As previously stated, Rowlands et al. teach that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that carries out the processing necessary to produce a fully functional antibody"). Thus, a person of ordinary skill in the art would know which parameters are critical to express an antibody in a

eukaryotic cell. Furthermore, Zauderer provides a facile method for expressing libraries using the same vaccinia virus that is presented in Rowlands et al. and, a result, one of ordinary skill would also know which parameters are critical to form a library in eukaryotic cells. Thus, a person of skill in the art would know how to form a library of antibodies. The proposition that a person of skill in the art would somehow "forget" how to do this when faced when with the task of producing a "second" library has no basis in fact. Furthermore, the courts have repeatedly held that the mere "duplication" or "scale up" (i.e., one library to two) is prima facie obvious unless some unexpected results are obtained (e.g., see *In re Rinehart*, 531 F.2d. 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976); see also see *In re Harza*, (274 F.2d 669, 124 USPQ 378 (CCPA 1960)), which is not the case here.

[12] Again, Applicants' arguments are not commensurate in scope with the claims. That is, even if, *assuming arguendo*, Applicants assertion that many antigen-binding region are difficult to assemble correctly as a fusion protein in bacterial cells (as opposed to mammalian cells), this would still leave those antigen-binding regions that are not difficult to assemble. Furthermore, the combined references of Zauderer et al. and Rowlands et al. teach the use of antibody libraries in mammalian cells for the reasons set forth in the rejection and arguments above. In addition, the Zauderer et al. reference, contrary to Applicants' assertions teaches the use of "multiple" libraries using vaccinia virus vectors (e.g., see Zauderer et al., page 49, last two paragraphs; see also figure 2 showing various constructs).

[13] In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must again be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so

long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In addition, "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *In re Gartside*, 203 F3d 1305, 1316, 53 USPQ2d 1769, 1776 (Fed. Cir. 2000) (citing *In re Dembiczak*, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "'[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" In re Beattie, 974 F.2d 1309, 1311-12, 24 USPQ2d 1040, 1042 (Fed. Cir. 1992) (quoting Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)). "[E]vidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. . . ." Dembiczak, 175 F.3d at 999, 50 USPQ2d at 1617 (citing Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996); Para-Ordnance Mfg. v. SGS Imports Int'l, Inc., 73 F.3d 1085, 1088, 37 USPQ2d 1237, 1240 (Fed. Cir. 1995)). Here, the references themselves, not Applicants' specification, provides ample motivation for their combination as set forth in the rejection above (e.g., see rejection above wherein "motivation" is explicitly correlated to each individual reference by page and line number).

Finally, Applicants have failed to assert that any of the reasoning set forth in the obviousness rejection above took into account knowledge gleaned only from applicants'

disclosure. To the contrary, Applicants merely stated that you couldn't combine the three references, presumably because there is no motivation to do so. In other words, it appears that applicants' hindsight argument is merely a general argument or assertion without substance.

[14] The Examiner respectfully disagrees. Applicants have again mischaracterized the holding in *Fine*. *In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). The Federal Circuit *in Fine* reversed the Board decision noting that Eads deliberately sought to avoid the use of nitrogen because the sulfur detector was adversely affected by substantial quantities of nitrogen stating, "instead of suggesting that the system be used to detect nitrogen compounds, Eads deliberately seeks to avoid them; it warns against rather than teaches Fine's invention." See *Id.* at 1599. Thus, *In re Fine* provides an example of a "teaching away" by disclosing that the presence of a claimed element, nitrogen, is undesirable. Thus, the decision was based on the "undesirable" nature of the nitrogen as shown by a comparison of the two prior art references, not an "under appreciation" of the special features of Applicants' claimed invention. Therefore, Applicants' arguments are not on point.

[15] The Examiner respectfully disagrees. Applicants' arguments are not commensurate in scope with the claims and neither is the Storkus declaration. Briefly, as state above and in previous office actions, the claims don't require most of the features described in the Storkus declaration (e.g., "good" antibodies, "efficient" selection, etc.). In fact, the two libraries don't even need to combine together at all. For example, Applicants' "capable of" limitation in claim 84, step (iii) has not been afforded patentable weight (see *In re Hutchison* argument above) and, as a result, it does not matter whether Dr. Storkus has expressed reservations about whether or not the prokaryotic system would somehow preclude their association. This would not prevent

the two libraries from being "capable" of associating together as in a mammalian system for example. In addition, the Storkus declaration is deficient for the additional reasons cited above (e.g., see sections [2], [3], [7] and [8] above).

[16] The Examiner respectfully disagrees. Each chain could bind to the antigen independently of one another (e.g., heavy-antigen-light as opposed to heavy/light-antigen). In addition, Applicants' never set forth any "condition" under which this "specificity" is to be measured or, alternatively, never set forth any "minimal level" of binding affinity. For example, simple dipole forces like hydrogen bonds would suffice to impart this minimal level of specificity. That is, all heavy/light chains would exhibit some level of "specificity" for antigens that contain "hydrogen bonds" (e.g., OH groups) as compared to molecules that do not (e.g., fullerenes). If this were not the case, then Applicants' claims would be missing an "essential step" in accordance with *In re Mayhew* (see *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976)) because, according to Applicants' admission above, the experiments could not be performed without this method step (i.e., actually combining the heavy and light chains together).

[17] Applicants arguments are again not commensurate in scope with the claims. Independent claim 84, for example, is not limited to screening only "unknown" antigens as erroneously purported. Furthermore, as noted above (e.g., see [16]), no "minimal" requirement has been set forth with regard to the level of specificity a particular immunoglobulin must exhibit toward an antigen. Therefore a *de minimis* showing is all that is required (i.e., all heavy/light chains will inherently qualify). In addition, the teachings in Rowlands are not "limited" to known antigens as purported. This narrow view of the reference is entirely unjustified.

Waterhouse explains at length how their current technology grew out of phage display, which was originally designed to "mimic" the immune systems to find antibodies directed against foreign antigens. Therefore, Applicants' arguments are without merit.

[18] The Examiner respectfully disagrees. In it Applicants who have failed to consider the claimed invention. Applicants state, for example, "antibodies produced in prokaryotic cells are not processed or assembled in the same manner as antibodies expressed in eukaryotic (e.g., mammalian) cells, and therefore may lose antigen specificity due to improper folding" (see above). However, Applicants' claims do not specify any particular antibody/antigen or class of antibodies/antigens. Therefore, the claims are not limited to only antibodies that might lose antigen specificity due to improper folding in eukaryotic systems. In addition, all of the Examiners previous arguments with respect to this issue are still applicable (e.g., see 4/21/06 Office action, page 31, section **[14]**; see also sections **[15]** and **[16]**).

[19] Again, Applicants' arguments are not commensurate in scope with the claims. The claims are not limited to "high affinity" antibodies or antibodies directed against "difficult targets" as set forth in Exhibit A2 (e.g., see page 34, top of page, "Companies thought this approach would be useful for a variety of targets for which they had been unsuccessful in generating high affinity antibodies"; see also title, "Interviewees also saw opportunities with our platform to screen difficult antigens"; see also responses like Susan Thorpe providing examples of "difficult" targets like non-proteins" (e.g., see Exhibit A2). Thus, Applicants have misrepresented exhibit A2 by stating that it broadly stands for the proposition of screening any "antigen specific" antibody when, in reality, it only provides evidence for "high affinity" antibodies directed against "difficult" targets.

[20] Exhibit B2 refers to a collaboration between OPi and Vaccinex for technologies concerning "monoclonal" antibodies directed against "difficult targets" for treating "rare haematological diseases." (e.g., see Exhibit B2). In contrast, Applicants' claims are not limited to "difficult" targets associated with "rare haematological diseases" (e.g., see independent claim 84 that does not limit the identity of the target whatsoever), nor are the limited to the use of "monoclonal" antibodies. In addition, Applicants' claims read on a "plurality" of first/second immunoglobulins, which would encompass as few as "two." This is clearly not what OPi is intending to collaborate on the discovery of monoclonal antibodies against "difficult targets" would be impossible (i.e., screening "two" at a time would take an eternity). Therefore, Applicants' arguments and exhibits are not commensurate in scope with the claims. In addition, Exhibit B2 does not refer to any of the claimed features. Exhibit B2 does not mention any o the claimed method steps. It also fails to mention most, if not all, of the other claimed features including, the use of (1) a v7.5/tk virus genome and a vEL/tk virus genome (e.g., claim 108), (2) use of a "second" library of polynucleotides (e.g., claim 84), (3) cleaving an isolated vaccinia virus genome to produce a first viral fragment and a second viral fragment (e.g., claim 107), (4) the use of "sub-pools" (e.g., see claim 115), etc. Therefore, there is no nexus (e.g., see *In re GPAC Inc.* (CAFC) 35 USPQ2d 1116 (6/20/1995), "Licenses taken under the patent in suit may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate 'a nexus between the merits of the invention and the licenses of record.' Stratoflex, 713 F.2d at 1539, 218 USPQ at 879; see Demaco, 851 F.2d at 1392, 7 USPQ2d at 1226."). Thus, exhibit B2 and Applicants' associated arguments are still deficient for the reasons outlined above even though the word "vaccinia" in mentioned in exhibit

B4. In addition, the Examiner's previous comments with regard to a "lack of interest" are still applicable (e.g., see 4/21/06 Office Action, pages 33 and 34, especially page 34, paragraph 1).

[21] The definition in the specification at paragraph 57 does not add support to Applicants' position. The definition is hedged with "exemplary" language (e.g., "generally comprising") and, as a result, does not require the particulars Applicants' refer to. In addition, even if, assuming arguendo, a narrow definition could be inferred, it would not overcome the nexus arguments set forth above (e.g., see section **[21]**).

[22] Again, we don't know what "innovative technology" is being referred to because Applicants' have not established a "nexus" to the claimed invention (see above).

[23] The evidentiary burden for secondary considerations rests with the Patentee. *In re Paulsen*, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994). Here, Applicant's arguments with regard to the "diversity of uses" do not rise to the level of factual evidence. See MPEP § 716.01(c): The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Therefore, Applicants' have not met their evidentiary burden.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

7. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent Application Pub. No. 2003/0104402 A1 (referred to herein as '402) (i.e., Application No. 10/052,942) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

Here, claims 1-84 of U.S. Patent No. '402 recite a method for selecting polynucleotides which encode immunoglobulin molecules which is essentially the same as that disclosed by claims 84, 88-97, 99, 103, 107-122 and 127-131 in the present application (e.g., both methods disclose eukaryotic host cells, a first and second library of polynucleotides encoding immunglobulin light/heavy chain constant/variable regions, permitting expression of said immunoglobulin molecules, contacting the molecules with an antigen, recovering the polynucleotides that encode for immunoglobulins that bind to said antigens, etc). The method of claims '402 differ from the present application in that they claim "intracellular" as opposed to "extracellular" expression.

However, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector i.e., "extracellular" expression (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a

polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence i.e., Rowlands et al. teach "extracellular" expression. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Thus, it would have been obvious to modify the method of claims 1-84 of U.S. Patent Pub. No. '402 such that "extracellular" expression was performed instead of

"intracellular" expression because Rowlands et al. teach that "extracellular" expression may be obtained within Applicants' preferred vaccinia virus vector. One having ordinary skill in the art would have been motivated to make such a modification because Rowlands et al. teach that their "extracellular" expression is particularly well suited for genes of mammalian origin (e.g., see page 4, first full paragraph), which is a preferred embodiment of the '402 patent application (e.g., see claim 26 of '402). In addition, Rowlands et al. teach that their "extracellular" expression techniques are advantageous "particularly in terms of versatility and speed [because] ... [the] virus will infect a wide range of cells [and] ... [thus] Cell lines suitable for production of a recombinant antibody can thus be derived conveniently and quickly. (e.g., see Rowlands et al., paragraph bridging pages 9-10). Furthermore, Rowland et al. teach that "extracellular" screening can be useful in tumor diagnosis and/or analysis (e.g., see page 9, lines 1-4; see also examples wherein Campath antigen is used). Finally, a person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is ***secreted into the medium*** and can thus be recovered in functional form").

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims 84, 88-97, 99, 103, 107-122 and 127-131 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application 10/465,808 (referred to herein as '808) (US 2005/196755) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) in view of Rowlands et al. (WO 93/01296) (Date of Patent is **January 21, 1993**) and Zauderer et al. (WO 00/28016) (Date of Patent is **May 18, 2000**). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examiner application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1986).

For ***claim 84, 88, 96-97, 113, 117***, the '808 application discloses a method for selecting polynucleotides which encode an antigen-specific human immunoglobulin molecule (e.g., see '808, claim 46). The '808 application also disclose **(a)** introducing into a population of mammalian host cells capable of expressing said immunoglobulin molecule and permissive for vaccinia virus infectivity (e.g., see claim 46, step (a); see also claim 80 disclosing the use of mammalian host cells which would inherently be permissive for vaccinia virus infectivity). The '808 application also discloses a first library of polynucleotides encoding through operable association with a transcriptional control region, a plurality of first immunoglobulin subunit polypeptides (e.g., see '808 application, claim 46, step (a); see also claims 59 and 68 disclosing constant heavy chain

region; see also claims 128). In addition, the '808 application discloses each first immunoglobulin subunit polypeptide comprising **(i)** a first immunoglobulin constant region selected from the group consisting of a heavy chain constant region and a light chain constant region (e.g., see '808, claim 46 claim 128, step (a)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of a heavy chain variable region and a light chain variable region wherein said variable region corresponds to said first constant region (e.g., see '808, claim 46(a)(ii);). The '808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said first immunoglobulin subunit polypeptide (e.g., see '808 claim 46(a)(iii)). The '808 application also discloses **(b)** introducing into said host cells a second library of polynucleotides encoding through operable association with a transcriptional control region a plurality of second immunoglobulin subunit polypeptides each comprising (e.g., see '808, claim 46(b); see also claim 80). In addition, the '808 application discloses **(i)** a second immunoglobulin constant region selected from the group consisting of a heavy chain constant region or a light chain constant region wherein said second immunoglobulin constant region is not the same as said first immunoglobulin constant region (e.g., see '808, claim 46(b)(i)). The '808 application also discloses **(ii)** an immunoglobulin variable region selected from the group consisting of heavy chain variable region ad a light chain variable region, wherein said variable region corresponds to said second constant region (e.g., see '808, claim 46(b)(ii). The'808 application also discloses **(iii)** a signal peptide capable of directing cell surface expression or secretion of said second immunoglobulin subunit (e.g., see '808, claim 46(b)(iii)). The '808 also

discloses said second immunoglobulin subunit polypeptide that is capable of combining with said first immunoglobulin polypeptide to form an immunoglobulin molecule (e.g., see claim 46(b)(iii)). Finally, the '808 application teaches (c)-(e) permitting expression of immunoglobulin molecules, contacting said immunoglobulin molecules with an antigen, detecting specific antigen-antibody complexes and recovering polynucleotides of said first library which encode immunoglobulin subunit polypeptides (e.g., see claim 46(b)(iii)).

For ***claims 89-91***, the '808 application disclose repetitive steps for "biopanning" a library (e.g., see '808, 48, 52, 115 and 123).

For ***claims 92-95***, the '808 application disclose "isolating" steps (e.g., see '808, see claims 49 and 53).

For ***claim 99***, the '808 application also discloses an MOI of 1 to 10 (e.g., see '808, claim 76).

For ***claim 103***, the '808 application also disclose T7 promoter (e.g., see '808 application, claim 96).

For ***claim 107, 110, 127-131***, the '808 application disclose method steps for "tri-molecular" recombination (e.g., see '808, claim 98, 99 and 128).

For ***claims 114-116, 118-120***, the '808 application disclose the use of virus "pools." (e.g., see '808, claims 113, 114, 119, 121)

The '808 differs from the claimed invention as follows:

For ***claim 84***, '808 fails to disclose the use of a vaccinia virus. The 808 application only discloses the use of a eukaryotic virus vector such as a poxvirus vector

vector (e.g., see '808, claims 72, 73, 78, 79 and 85-88).

For ***claims 108-109, 111-112***, the '808 application fails to disclose v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction sites.

For ***claims 121-122***, the '808 application fail to disclose ELISA (e.g., see page 18, line 7).

However, Rowlands et al. and Zauderer et al. teach the following limitations that are deficient in abc et al.:

For ***claim 84***, Rowlands et al. and Zauderer et al. (see entire documents) teach the use of vaccinia virus. For example, Rowlands et al. teach a method for producing antibodies in vaccinia infected cells that reads on the presently claimed invention (e.g., see Rowlands et al., abstract). Furthermore, Rowlands et al. teach the use of a population of mammalian host cells (e.g., see page 4, paragraph 2; see also paragraph bridging pages 7-8) for introducing and expressing a first/second polynucleotide encoding, through operable association with a transcriptional control region a first/second immunoglobulin polypeptide comprising both heavy/light chain constant/variable regions and a signal peptide for secretion using a vaccinia virus vector (e.g., see claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter"; see also page 2, middle paragraph, "An antibody molecule is composed of two light chains and two heavy chains ... Each heavy chain has at one end a variable domain followed by a number of constant domains, and each light chain has a variable domain at one end and a constant domain at the other end"; see

especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"; see also page 6, paragraphs 1 and 2). Rowlands et al. do not explicitly state that a "signal" peptide is being used, but the Examiner contends that this feature is inherent in the method disclosed by Rowlands et al. because the fully functional recombinant antibody would not be "secreted" unless it has such a sequence. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, Rowlands et al. disclose contacting said immunoglobulin molecules with an antigen and detecting specific antigen-antibody complexes (e.g., see pages 18-19 and Table I wherein the Campath 1H antigen was "contacted" with said immunoglobulin molecules and "detection" was carried out using both T-cell and antigen binding assays). Finally, Rowlands et al. disclose recovering the vaccinia virus vectors containing polynucleotides of said first library which encode immunoglobulin subunits polypeptides which, as part of an immunoglobulin molecule are specific for said antigen (e.g., see page 5, paragraph 1, step 4, wherein the virus is "harvested" several times [i.e., recovered and/or isolated]).

In addition, Zauderer et al. (see entire documents) teach the use of a "library" of polynucleotides in a vaccinia virus vector using the "tri-molecular recombination" approach for screening purposes (e.g., see Zauderer et al., page 52, lines 13-16, "The high yield of viral recombinants in tri-molecular recombination makes it possible, for the first time, to efficiently construct genomic or cDNA libraries in a vaccinia virus derived vector"; see also page 15, paragraph 1; see also page 22, last two paragraphs; see also Example 6 on pages 42-52). In addition, Waterhouse et al. teach that a "library" can be usefully employed to screen for antibodies with high affinity to various antigens including the use of heavy/light chains that are "packaged together" i.e., two libraries (see Waterhouse et al., page 2265, column 1; see also paragraph bridging pages 2265-2266, "... creation of extremely large combinatorial repertoires [is possible]... for example by providing a light chain repertoire in A [i.e., library number 1] and a heavy chain repertoire in B [i.e., library number 2]"). The Examiner further notes that Applicants' elected mammalian "HeLa" cells are disclosed also by Zauderer et al. (e.g., see Zauderer et al., page 32, line 2).

For ***claims 89-91***, Zauderer et al. also disclose the use of vaccinia virus library vectors that require the use of a helper virus (i.e., are "incapable of producing infectious vaccinia virus") to infect host cells (e.g., see Zauderer et al., paragraph bridging pages 97-98, "Vaccinia virus DNA is not infectious as the virus cannot utilize cellular transcriptional machinery ... Previously ... non-homologous poxvirus fowlpox ... have been utilized as helper virus for packaging"). Zauderer et al. also indicate that the steps for introducing said vectors into host cells, permitting the expression of said vectors,

contacting said expressed antibodies with an antigen and recovering said vectors can be repeated as needed to increase the specificity and/or binding affinity (e.g., see page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure").

For ***claims 92-95***, Zauderer et al. also disclose "isolating" the polynucleotides contained in the vaccinia virus vectors (e.g., see Zauderer et al., page 52, lines 20-23; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claim 99***, Zauderer et al. also disclose, for example an MOI = 1 (e.g., see page 86, line 2).

For ***claim 103***, Rowlands et al. also disclose a T7 phage promoter active in cells in which T7 RNA polymerase is expressed (e.g., see page 8, paragraph 2, "Expression levels of the two chains of the antibody can be enhanced by use of T7 polymerase to amplify the gene under the control of the T7 promoter").

For ***claims 107, 110, 127-131***, Zauderer et al. also disclose "tri-molecular" recombination, which includes, for example, cleavage of v7.5/tk or vEL/tk virus genomes with NotI/ApaI restriction enzymes and "one" transfer plasmid containing TKL/TKR and a library of human immunoglobulin genes containing both heavy and light genes to form vaccinia virus vectors via homologous recombination and method steps for screening and purifying said vectors repeated as many times as are needed to produce the desired

products (e.g., see pages 48-52, sections 5.2-5.3; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]"; see also claim 9, "A process ... compris[ing] ... transfecting the infected cells with a transfer vector [i.e., introducing a polynucleotide] containing DNA encoding the light and ... heavy chain of the antibody under control of a suitable promoter").

For ***claims 108, 111***, Zauderer et al. disclose both v7.5/tk and vEL/tk (e.g., see figure 1).

For ***claims 109, 112***, Zauderer et al. disclose both NotI and ApaI (e.g., see figure 10).

For ***claims 114-116, 118-120***, Zauderer et al. also disclose the use of "virus pools" (e.g., see page 51, last paragraph, especially line 27; see also page 58, Table V wherein multiple cycles are disclosed; see also page 23, last paragraph through page 24, first paragraph, especially lines 8-10, "The above-described protocol is repeated or more cycles, to increase the level of enrichment obtained by this procedure [i.e., involves combining isolated fractions]").

For ***claims 121-122***, Rowlands et al. disclose ELISA (e.g., see page 18, line 7).

It would have been *prima facie* obvious to one of ordinary skill in the art to select vaccinia virus as taught by the combined references of Zauderer et al. and Rowlands et al. as the eukaryotic virus vector as taught by the '808 patent application because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular

recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.). Thus, one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. and the'808 application because Zauderer et al. explicitly state that the their "tri-molecular" approach represents an easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. (e.g., see Zauderer et al., page 22, lines 14-17, "Major advantages of these infectious [vaccinia] viral vectors are ... the ease and efficiency with which recombinants can be introduced mammalian cells"; see also Rowlands et al., page 4, paragraph 2, "One advantage of this system is the authenticity of gene products, particularly those requiring processing and post-translational modification such as glycosylation. This may be particularly important for genes of mammalian origin"). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and the '808 application. Furthermore, a person of ordinary skill in the art would reasonably have expected to be successful because Rowlands et al. state that the use of vaccinia virus as vectors is well known and has wide applications and explicitly state that it can be used for antibody production (e.g., see Rowland et al., page 4, first full paragraph, "The use of vaccinia virus as a vector for expression of foreign genes has been employed for almost a decade ..."; see also paragraph bridging pages 9 and 10, "the versatility of the method to the present invention means that it will usually be possible to select a type of cell that

carries out the processing necessary to produce a fully functional antibody") and also provide successful examples of antibody expression using vaccinia.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

9. Applicant's arguments directed to the above double patenting rejection were fully considered but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "One of ordinary skill in the art would not have had a reasonable expectation of success in combining Rowlands with the '402 publication to arrive at the present invention. Rowlands describes the use of vaccinia virus vectors for making an individual recombinant antibody, not an immunoglobulin expression library. There would have been no indication to one of ordinary skill in the art that the methods for making or screening a library of intracellularly expressed immunoglobulins, as described in the '402 publication could be used to make or screen a library of extracellularly expressed immunoglobulins as in the present invention based on the disclosure in Rowlands of an individual antibody that is expressed extracellularly. The Examiner is improperly focusing on the obviousness of differences and substitutions in making this rejection rather than on the invention as a whole. See Hybritech, 802 F.2d at 1383. Selection of previously unknown polynucleotides from the intracellular expression of two libraries of immunoglobulin heavy and light chains as disclosed in the '402 application is

different than the expression of a single, previously selected antibody that is secreted into the culture medium as in Rowlands. Applicants respectfully submit that, as with respect to making a prima facie case of obviousness under 35 U.S.C. Section 103, it is improper "to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the fill appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" In re Hedges, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685 (Fed. Cir. 1986) (quoting In re Wesslau, 353 F.2d 238, 241 147, U.S.P.Q. 39 1,393 (CCPA 1965)). Reconsideration and withdrawal of the rejection therefore are respectfully requested" (e.g., see 7/25/06 Response, pages 48-50).

[2] Applicants argue that the two double patenting rejections be held in abeyance (e.g., see 7/25/06 Response, page 50).

This is not found persuasive for the following reasons:

[1] The Examiner respectfully disagrees. A person of skill in the art would have reasonably expected to be successful because Rowlands et al. explicitly state that the vaccinia virus vectors used in '402 can be manipulated to secrete antibodies (e.g., see especially page 4, second full paragraph, "It has now been found that vaccinia virus vectors [i.e., the animal virus disclosed in '402] can be used for expression of the light and heavy chains of a recombinant antibody in a suitable host cell and that a proportion of the chains combine within the cell to form a recombinant antibody which is secreted into the medium and can thus be recovered in functional form"). Adding a "signal" sequence to the libraries disclosed in the '402 would be well within the ordinary level of skill of a practicing artisan. See also arguments above directed

to the "invention as a whole" and "picking and choosing", which are incorporated in their entirety herein by reference.

[2] The provisional rejections will not be held in abeyance (e.g., see MPEP § 804 B. Between Copending Applications—Provisional Rejections, "The 'provisional' double patenting rejection ***should continue to be made by the examiner*** in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications."). Here, a double patenting rejection is NOT the only rejection remaining in one of the applications and thus the double patenting rejection is proper.

Accordingly, the double patenting rejections cited above are hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 6, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER